Ketamine concentrations during cardiopulmonary bypass

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Purpose: *To describe the serum concentrations of ketamine following a clinically relevant dosing schedule during cardiopulmonary bypass (CPB).*

Methods: *Design: Prospective case series. Setting: Tertiary care teaching hospital. Patients: Six patients undergoing coronary artery bypass grafting and over age 60 yr. Intervention: Following induction of anaesthesia each patient received a bolus of ketamine 2 $mg \cdot kg^{-1}$ followed by an infusion of 50 $\mu g \cdot kg^{-1} \cdot min^{-1}$ which ran continuously until two hours after bypass. Main Outcome Measures: Ketamine serum concentrations were measured at five minutes after bolus, immediately following aortic cannulation, 10 and 20 min on CPB, termination of CPB, termination of the drug infusion and three and six hours after infusion termination.*

Results: *At the time of aortic cannulation, ketamine concentrations were 3.11 ± 0.81 $\mu g \cdot ml^{-1}$, these levels decreased by one third with the initiation of CPB. By the end of CPB the concentrations had returned to levels roughly equivalent to those observed at the time of aortic cannulation. Following cessation of the infusion, ketamine concentration declined in a log-linear fashion with a half-life averaging 2.12 hr. (range 1.38–3.09 hr).*

Conclusions: *This dosage regimen maintained general anaesthetic concentrations of ketamine throughout the operative period. These levels should result in brain tissue concentrations in excess of those previously shown to be neuroprotective in animals. Thus we conclude that this infusion regimen would be reasonable to use in order to assess the potential neuroprotective effects of ketamine in humans undergoing CPB.*

Objectif: *Faire connaître les concentrations sériques de la kétamine procurées par un schéma posologique approprié à la circulation extracorporelle (CEC).*

Méthodes: *Type d'étude: Prospective. Endroit: Hôpital de soins tertiaires et d'enseignement. Patients: revascularisation du myocarde chez six patients âgés de plus de 60 ans. Intervention: Après l'induction de l'anesthésie chacun des patients a reçu un bolus de kétamine 2 $mg \cdot kg^{-1}$ suivi d'une perfusion de 50 $\mu g \cdot kg^{-1} \cdot h^{-1}$ en permanence, arrêtée deux heures après l'intervention. Principales mesures de résultats: Les concentrations sériques de kétamine mesurées après la canulation de l'aorte, 10 et 20 min après le début de la CEC, à l'arrêt de la CEC et trois et six heures après l'arrêt de la perfusion.*

Résultats: *Les concentrations de kétamine qui étaient de 3,11 ± 0,81 $\mu g \cdot ml^{-1}$ au moment de la canulation de l'aorte ont diminué du tiers avec le début de la CEC. A la fin de la CEC, elles sont revenues à peu près à ce qu'elles étaient au moment de la canulation de l'aorte. Après l'arrêt de la perfusion, la concentration de la kétamine a diminué de façon linéaire logarithmique avec une demi-vie moyenne de 2,12 h (écart de 1,38 à 3,09h).*

Conclusions: *Ce schéma posologique a permis de maintenir des concentrations anesthésiques de kétamine pendant l'intervention. Ces niveaux devraient produire des concentrations cérébrales plus élevées que celles qui ont été démontrées comme neuroprotectrices chez l'animal. Les auteurs concluent que ce schéma devrait être pertinent pour l'évaluation des propriété neuroprotectrices de la kétamine chez les humains qui subissent une CEC.*

Key Words
ANAESTHETICS, INTRAVENOUS: ketamine;
PHARMACOLOGY: pharmacokinetics;
SURGERY: cardiac, cardiopulmonary bypass.

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Neurological injury is an important cause of morbidity and mortality after cardiac surgery.[1-3] Research to date suggests that the majority of this injury is due to embolic ischaemia.[4-9] There is much evidence that excitotoxicity is integral to the pathophysiology of ischaemic neuronal injury. The mechanisms involve the ischaemia-induced release of excitatory amino acids which,

through agonist activity at the n-methyl-d-aspartate (NMDA) receptors, result in neuronal swelling and eventually an increase in intracellular calcium.[10,11] In models of focal neuronal ischaemia NMDA receptor antagonists are effective in reducing injury, particularily when administered prior to ischaemic insult. Thus NMDA antagonists, administered throughout the operative period may offer potential benefits.

Many of the NMDA antagonists are not ready for human trial or have other contraindicated physiological effects. Ketamine is a non-competitive NMDA antagonist and has demonstrated neuroprotective properties in models of focal cerebral ischaemia.[12–14] While ketamine has proved to be safe in the anaesthetic armamentarium for coronary artery bypass grafting (CABG) surgery[15,16] there is no information available on the effect of cardiopulmonary bypass (CPB) on ketamine drug concentrations. To assess the potential neuroprotective effects of ketamine, this information is important. Accordingly, this study was designed to describe the serum concentrations of ketamine following a clinically relevant dosing schedule during CABG surgery involving CPB, and to determine if these doses would achieve serum concentrations associated with neuroprotection in animals.

Methods

After obtaining the approval of the institutional ethics review board, written informed consent was obtained from six patients >60 yr undergoing CABG. Patients were premedicated with diazepam (0.1 $mg \cdot kg^{-1}$ *po*) or lorazepam (0.03 $mg \cdot kg^{-1}$ *sl*), and morphine sulfate (0.15 $mg \cdot g^{-1}$ *im*) with perphenazine (0.05 $mg \cdot kg^{-1}$ *im*). Anaesthesia was induced with fentanyl (10–15 $\mu g \cdot kg^{-1}$), midazolam (0.05 $mg \cdot kg^{-1}$) pancuronium (0.15 $mg \cdot kg^{-1}$). After intubation and placement of a pulmonary artery catheter, heart rate (HR), mean arterial pressure (MAP), mean pulmonary artery pressure (PAP) and thermodilution cardiac outputs (CO) were recorded. Ketamine (2 $mg \cdot kg^{-1}$) was then given *iv* followed by an infusion (50 $\mu g \cdot kg^{-1} \cdot min^{-1}$). Simultaneously, an infusion of midazolam was started at 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Both infusions ran throughout CPB and for two hours after CPB. Halothane was used for supplemental anaesthesia as deemed necessary by the attending anaesthetist in the pre- and post-bypass periods. Repeat haemodynamic measurements were performed 10 min after completion of the ketamine bolus and at the time of aortic cannulation. Blood samples were drawn at five minutes after the bolus, aortic cannulation, 10 and 20 min on CPB, termination of CPB, termination of the drug infusion and three and six hours after infusion termination. Patients were interviewed on day four after surgery and asked about dreams or hallucinations during the perioperative period.

A Cobe heart-lung machine with Bentley tubing and reservoirs was used for CPB, including membrane oxygenators (Bard HF5400) and in-line arterial line filters (Bard H-645 with Biothyl). Circuit prime consisted of 2000 ml lactated Ringer's solution, 100 ml albumin 25% , 25 g mannitol, 50 meq sodium bicarbonate, and 5000 U heparin sodium. Priming solution was precirculated through a 5 μm prebypass filter (Bentley) before cannulation. Haematocrit was maintained >20% during CPB with the addition of blood as necessary. Nonpulsatile flows of 2.4 $L \cdot min^{-1} \cdot m^{-2}$ were used at normothermia and were no lower than 1.8 $L \cdot min^{-1} \cdot m^{-2}$ at 30°C. Target nasopharyngeal temperatures were 30–34°C. Mean arterial pressure was maintained >50 mmHg, with phenylephrine if necessary, and hypertension (>90 mmHg) was treated with Isoflurane up to a maximum concentration of 1%, followed by the addition of sodium nitroprusside if required. Oxygen inflow of 2–5 $L \cdot min^{-1}$ was adjusted for normal oxygenation and alpha-stat acid-base balance.

Blood samples were immediately placed on ice and centrifuged within three hours of sampling. The plasma supernatant was stored frozen at –20°C. Ketamine concentrations in plasma were determined by a liquid chromatographic method developed and validated in our laboratory. Briefly, this method involved extraction of ketamine from 0.5 ml of plasma with 2.0 ml of methylene chloride. The organic phase was evaporated to dryness and reconstituted with 0.2 ml of mobile phase and 0.1 ml was injected directly into the chromatographic system. The chromatographic system consisted of a Spectra Physics SP4200 liquid chromatographic pump which pumped a mixture of acetonitrile 46% and 0.05M H_3PO_4 54% containing 0.01 molar sodium lauryl sulphate at 2.0 $ml \cdot min^{-1}$ through a 5 μm 4.6 mm × 250 mm Beckman Ultrasphere reverse phase column. The column effluent was monitored at 210 nm using an ultraviolet detector.

Ketamine eluted at approximately 11 min. Standard curves were linear in the range from zero to 10 $mg \cdot L^{-1}$ and the limit of quantification was 0.05 $mg \cdot L^{-1}$. Over this range the error on duplicate determinations, as determined by the coefficient of variation, averaged <8%.

Data analysis was done using JMP, (SAS Institute, Inc., Carey NC). Ketamine concentrations at each sampling time were averaged and 95% confidence intervals were generated. The half life following cessation of the infusion was calculated by a standard equation.[18] Haemodynamic variables were compared using one way ANOVA. All data are reported as mean ± standard deviation.

TABLE I Patient characteristics

Study No.	*Age (years)*	*Sex*	*LV function* (grade)*	*No. of bypasses*	*CPB duration (minutes)*	*Infusion duration (minutes)*	*Total ketamine dose (mg)/ (mg·kg^{-1})*
1	60	Male	I	3	117	338	1864/(18.9)
2	74	Male	III	3	140	338	1325/(18.9)
3	78	Male	I	2	78	240	1219/(14)
4	77	Male	II	3	100	277	1205/(15.9)
5	61	Male	I	3	100	303	1326/(17.2)
6	69	Male	I	2	64	279	1276/(16.0)

*LV function = left ventricular function. Grade I = Left ventricular ejection fraction (LVEF) >60%, Grade II = LVEF 40–60%, Grade III = LVEF 20–40%, Grade IV = LVEF <20%.

TABLE II Mean haemodynamic variables

	HR (SD)	*MAP (SD)*	*PAP (SD)*	*PCWP (SD)*	*CO (SD)*
Pre-Bolus	54.7 (8.5)	76.3 (8.7)	13.7 (1.9)	6.3 (1.8)	4.0 (0.5)
Post-Bolus	63.0* (16.6)	99.2 (10.0)*	14.8 (3.1)	7.3 (3.1)	4.0 (1.1)
Pre-Bypass	58.0 (9.7)	66.3 (12.2)	11.0 (3.7)	4.3 (3.1)	3.8 (1.2)

HR = heart rate, MAP = mean arterial pressure in mmHg, PAP = mean pulmonary artery pressure in mmHg, PCWP = pulmonary capillary wedge pressure in mmHg, CO = cardiac output in litres/minute. (SD) = standard deviation.
*$P < 0.05$ vs pre-bolus and pre-ypass.

TABLE III Mean serum ketamine concentrations

Sample time	*Mean serum concentration mg·L^{-1} (SD)*	*Lower 95% C.I.*	*Upper 95% C.I.*
Post bolus	1.60 (1.01)	0.54	2.66
Aortic cannulation	3.11 (0.81)	2.26	4.00
CPB 10 min	2.39 (1.37)	0.94	3.83
CPB 20 min	2.34 (0.70)	1.61	3.07
CPB end	3.27 (0.73)	2.50	4.04
Infusion end	2.92 (1.35)	1.50	4.34
3 hr post	0.71 (0.71)	0.51	0.91
6 hr post	0.35 (0.14)	0.21	0.51

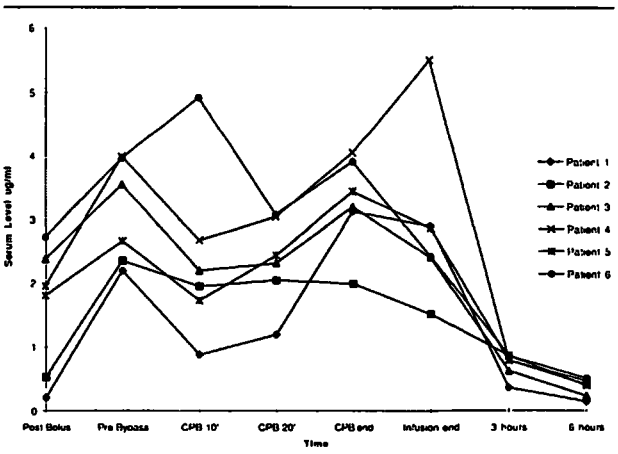

FIGURE Plot of serum concentrations of ketamine (μg·ml^{-1}) at study sample times for each individual patient. Post bolus sample was taken five minutes after the initial dose. The pre bypass sample was taken at the time of aortic cannulation. CPB 10', CPB 20', and CPB end were taken at 10 and 20 min after initiation of cardiopulmonary bypass and at the termination of cardiopulmonary bypass respectively. Infusion end, three hours, six hours were taken at the time of infusion termination, and three and six hours post termination respectively.

Results

Patient demographics are shown in Table I. The mean age of the patients studied was 69.8 ± 7.9 yr. Table II shows the haemodynamic variables. The MAP increased after the administration of ketamine and returned to normal by the time of aortic cannulation. No other change in HR, MAP, PAP, PCWP or CO was seen. Mean serum ketamine concentrations ± the 95% confidence interval are shown in Table III, and individual drug concentrations are shown in the Figure. At the time of aortic cannulation, the ketamine concentration averaged 3.11 mg·L^{-1}, ten minutes following CPB the concentration was reduced by approximately one-third in five of six patients and a 25% increase in concentration was observed in the sixth subject. During CPB these concentrations roughly doubled in four of these five subjects with the fifth showing no change in concentration such that the end-of-CPB concentrations were similar to concentrations observed at the time of aortic cannulation. The sixth patient, whose serum concentration increased

at the initiation of CPB, demonstrated a gradual decline to a concentration equivalent to that of aortic cannulation by the end of CPB. Following cessation of the infusion, the ketamine concentration declined in a log-linear fashion with a half-life averaging 2.12 hr (range 1.38 to 3.09 hours). Within three hours after cessation of the infusion concentrations averaged 0.71 $mg \cdot L^{-1}$ (range 0.35 to 0.85 $mg \cdot L^{-1}$).

Two of six patients reported dreams/hallucinations in the postoperative period. In one the dream occurred on the third postoperative day. The other patient's dreams and visual hallucinations occurred in the immediate preoperative period, both outside the operating room and up until induction. Postoperatively this patient reported visual hallucinations on the second postoperative day.

Discussion

Ketamine has been used as an anaesthetic agent during cardiac surgery for several years. The dosages used have varied widely, with infusion rates ranging from 12 to 90 $\mu g \cdot kg^{-1} \cdot min^{-1}$.[18] Reported infusion rates for general surgery also vary over a similiar range, with no clear guidelines.[18] There are no data available on the pharmacokinetic behaviour of ketamine in the setting of attained CPB. The dosage chosen by us was in the middle of those previously reported. The serum concentrations during the infusion were comparable with those in patients receiving similiar infusion rates, undergoing major abdominal surgery.[18] Serum levels were below those compatible with obeying simple commands (1 $mg \cdot L^{-1}$)[20] within three hours of stopping the infusions.

Cardiopulmonary bypass results in a number of physiological changes which will affect the distribution and metabolism of drugs.[21] Haemodilution would be expected to result in an increase in the volume of distribution and a fall in serum drug concentration. Not surprisingly, initiation of CPB was associated with a sharp decrease in serum ketamine levels. As CPB progressed, the concentrations gradually increased and by the end of CPB were at a level comparable with those seen at the time of aortic cannulation. There are a couple of mechanisms which may account for this. Hepatic blood flow decreases during CPB and this would affect the clearance of a drug such as ketamine.[21] The observed doubling of the ketamine concentration in four of the six patients is compatible with a reduced clearance during CPB. As well, redistribution from the tissues is an important mechanism in the rise of drug concentrations seen during bypass. This effect is particularily important for drugs with a large volume of distribution, such as ketamine.[21] While changes in protein binding do occur during CPB,[21] very little data exist on the protein binding characteristics of ketamine during CPB. Thus it is impossible to speculate on what effect these changes might have on the clearance of ketamine during CPB. The elimination half life in the post operative period of 2.12 hrs agrees closely with the mean half lives of 2.17–2.32 hr reported by Domino *et al.*[20]

Midazolam was administered to ablate the tachycardia and hypertension associated with ketamine and prevent unpleasant dreams/hallucinations.[22] Reich *et al.* found no increase in MAP in patients 8 and 13 min after induction with midazolam 0.2 $mg \cdot kg^{-1}$ and ketamine 2 $mg \cdot kg^{-1}$.[23] In this study we found a rise in the MAP ten minutes after the bolus. However, this often corresponded to the onset of surgical stimulation, making this finding difficult to interpret.

There is extensive *in vitro* and *in vivo* evidence that NMDA receptor antagonists, including ketamine, are neuroprotective.[12–14] The ketamine concentration required in human cerebral tissues for neuroprotection is unknown. In a rat model of cerebral ischaemia, anaesthetic doses of ketamine have neuroprotective effects.[13] Subanesthetic dosages in rats (1–2 $mg \cdot kg^{-1}$ *iv*) have also been found to block excitation of neurons by NMDA.[24] In tissue culture, 1 μM (0.24 $mg \cdot L^{-1}$) solutions of ketamine have been demonstrated to increase the rate of ATP recovery after an ischaemic insult.[25] Thus if one were to study the potential neuroprotective effects of ketamine in humans, a tissue concentration >0.24 $mg \cdot L^{-1}$ would seem a reasonable target. Ketamine itself is quite lipid soluble, rat brain tissue levels of ketamine are 2.5–4 times that of serum.[26,27] In humans there is very little information regarding the distribution of ketamine in the tissues. However in a case of an intraoperative death occurring 40 min after a single 100 mg dose of ketamine, brain tissue concentrations exceeded serum concentrations by a ratio of 1.33:1.[28] Thus it would seem reasonable to assume that the brain tissue levels during the infusion in these patients, were at least four times those shown to be neuroprotective in tissue culture.

In summary, ketamine administered as a 2 $mg \cdot kg^{-1}$ bolus, followed by an infusion of 50 $\mu g \cdot kg^{-1} \cdot min^{-1}$ provided anaesthetic serum concentrations in patients undergoing CPB. A transient in serum concentrations of ketamine occured with the onset of CPB, most likely due to the acute haemodilution resulting from the CPB priming solution. As bypass progressed, the serum concentrations increased to the pre-CPB levels. The serum levels seen in these patients throughout the procedure would likely result in brain tissue concentrations in excess of the 0.24 $mg \cdot L^{-1}$ previously shown to be neuroprotective in animals. We conclude that this infusion regimen would be reasonable to administer to assess the potential neuroprotective effects of ketamine in humans.

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